Remarks

Claims 130-152 are now pending in this application. Claims 130 and 138 are currently amended, without prejudice or disclaimer of any previously claimed subject matter. New dependent claims 144-152 have been added.

Rejections under 35 USC § 102

The Examiner has rejected claims 130-133 and 135-143 as being anticipated by U.S. 6,777,395 to Bhat et al. (Bhat).

The priority documents for Bhat are provisional application no. 60/344,528 filed on October 25, 2001, provisional application no. 60/299,320 filed on June 19, 2001, provisional application no. 60/282,069 filed on April 6, 2001 and provisional application no. 60/263,313 filed on January 22, 2001. The present application claims earliest priority to U.S. provisional application no. 60/206,585, filed on May 23, 2000, predating the earliest priority document of Bhat by eight months.

Support for the pending claims can be found throughout provisional application 60/206,585, a copy of which is attached. Specifically, the compound with formula VI on page 23 discloses a β-D-2'-methyl ribofuranosyl nucleoside, wherein base is a purine or pyrimidine base, R^4 may be alkyl, and R' may be H. The definition of alkyl on page 46 of the provisional application defines alkyl as a saturated hydrocarbon of C_1 to C_{10}, and specifically includes methyl.

Support for a method for the treatment of a hepatitis C virus infection in a host comprising administering the compounds recited in the claims in combination or alteration with a second anti-hepatitis C agent can be found on page 16, paragraph 2 to page 18 paragraph 1 and on page 49, paragraph 3 to page 51, paragraph 4 of the '585 provisional application. Interferon and ribavirin are specifically identified as second agents on page 49, heading II (1). Protease inhibitors are disclosed on page 49, heading II (2); a thiazolidine derivative is disclosed on page 50, heading II (4); a polymerase inhibitor is disclosed on page 50, heading II (9); and a helicase inhibitor is disclosed on page 50, heading II (8) of the '585 provisional application.

Pharmaceutical compositions are described on page 58, paragraph 2 to page of the provisional application. An oral dosage form containing 50-1000 mg is specifically described on page 58, paragraph 5. Tablet and capsule dosage units are disclosed on page 59, paragraph 2.

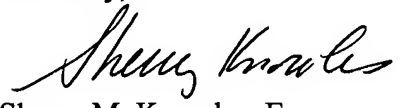
Disclosure of the purity of β-D-2'-methyl-ribofuranosyl nucleosides recited in the claims 142 and 143 can be found on page 47, paragraph 5 to page 48, paragraph 2 of the '585 provisional application. The application discloses that the definition of "substantially free of" or "substantially in the absence of" refers to a nucleoside composition that is at least 85% or 90% by weight, preferably 95% to 98% by weight, and even more preferably 99% to 100% by weight of the designated enantiomer of the nucleoside.

Rejections under 35 USC § 103

The Examiner has rejected claims 130-143 as obvious over U.S. 6,777,395, Bhat et al. As discussed above, provisional application no. 60/206,585, filed on May 23, 2000, predates the earliest priority of Bhat by eight months and provides support for the pending claims.

Withdrawal of the outstanding rejections is respectfully requested. The Commissioner is authorized to charge any fee associated with this Amendment, as well as any other deficiency, to Deposit Account 11-0980.

Sincerely,



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Attorney Docket No.: 06171.105001
PATENT

PROVISIONAL APPLICATION

FOR

UNITED STATES LETTERS PATENT

FOR

METHODS AND COMPOSITIONS FOR TREATING HEPATITIS C VIRUS

BY

Jean-Pierre Samadossi, a citizen of the United States of America residing at Birmingham Alabama, USA.

METHODS AND COMPOSITIONS FOR TREATING HEPATITIS C VIRUS

FIELD OF THE INVENTION

This invention is in the area of pharmaceutical chemistry, and is in particular, is a method and composition for the treatment of hepatitis C.

BACKGROUND OF THE INVENTION

The hepatitis C virus (HCV) is the leading cause of chronic liver disease worldwide. (Boyer, N. *et al. J. Hepatol.* 32:98-112, 2000). HCV causes a slow growing viral infection and is the major cause of cirrhosis and hepatocellular carcinoma (Di Besceglie, A. M. and Bacon, B. R., *Scientific American*, Oct.: 80-85, (1999); Boyer, N. *et al. J. Hepatol.* 32:98-112, 2000). An estimated 170 million persons are infected with HCV worldwide. (Boyer, N. *et al. J. Hepatol.* 32:98-112, 2000). Cirrhosis caused by chronic hepatitis C infection accounts for 8,000-12,000 deaths per year in the United States, and HCV infection is the leading indication for liver transplant.

HCV is known to cause at least 80% of posttransfusion hepatitis and a substantial proportion of sporadic acute hepatitis. Preliminary evidence also implicates HCV in many cases of "idiopathic" chronic hepatitis, "cryptogenic" cirrhosis, and probably hepatocellular carcinoma unrelated to other hepatitis viruses, such as Hepatitis B Virus (HBV). A small proportion of healthy persons appear to be chronic HCV carriers, varying with geography and other epidemiological factors. The numbers may substantially exceed those for HBV, though information is still preliminary; how many of these persons have subclinical chronic liver disease is unclear. (The Merck Manual, ch. 69, p. 901, 16th ed., (1992)).

HCV has been classified as a member of the virus family Flaviviridae that includes the *genera* flaviviruses, pestiviruses, and hapaceiviruses which includes hepatitis C viruses (Rice, C. M., Flaviviridae: The viruses and their replication. *In*: Fields Virology, Editors: Fields, B. N., Knipe, D. M., and Howley, P. M., Lippincott-Raven Publishers, Philadelphia, PA, Chapter 30, 931-959, 1996). HCV is an enveloped virus containing a positive-sense single-stranded RNA genome of approximately 9.4kb. The viral genome consists of a 5' untranslated region (UTR), a long open reading frame encoding a polyprotein precursor of approximately 3011 amino acids, and a short 3' UTR. The 5' UTR is the most highly conserved part of the HCV genome and is

important for the initiation and control of polyprotein translation. Translation of the HCV genome is initiated by a cap-independent mechanism known as internal ribosome entry. This mechanism involves the binding of ribosomes to an RNA sequence known as the internal ribosome entry site (IRES). An RNA pseudoknot structure has recently been determined to be an essential structural element of the HCV IRES. Viral structural proteins include a nucleocapsid core protein (C) and two envelope glycoproteins, E1 and E2. HCV also encodes two proteinases, a zinc-dependent metalloproteinase, encoded by the NS2-NS3 region, and a serine proteinase encoded in the NS3 region. These proteinases are required for cleavage of specific regions of the precursor polyprotein into mature peptides. The carboxyl half of nonstructural protein 5, NS5B, contains the RNA-dependent RNA polymerase. The function of the remaining nonstructural proteins, NS4A and NS4B, and that of NS5A (the amino-terminal half of nonstructural protein 5) remain unknown.

A significant focus of current antiviral research is directed toward the development of improved methods of treatment of chronic HCV infections in humans (Di Besceglie, A. M. and Bacon, B. R., *Scientific American*, Oct.: 80-85, (1999)). Currently, there are two primary antiviral compounds, Ribavirin and interferon-alpha, which are used for the treatment of chronic HCV infections in humans.

Treatment of HCV Infection with Ribivarin

Ribavirin (1-β-D-ribofuranosyl-1-1,2,4-triazole-3-carboxamide) is a synthetic, non-interferon-inducing, broad spectrum antiviral nucleoside analog sold under the trade name, Virazole (The Merck Index, 11th edition, Editor: Budavari, S., Merck & Co., Inc., Rahway, NJ, p1304, 1989). United States Patent No. 3,798,209 and RE29,835 disclose and claim Ribavirin. Ribavirin is structurally similar to guanosine, and has in vitro activity against several DNA and RNA viruses including falviviridae (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000).

Ribavirin reduces serum amino transferase levels to normal in 40% or patients, but it does not lower serum levels of HCV-RNA (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000). Thus, Ribavirin alone is not effective in reducing viral RNA levels. Additionally, Ribavirin has significant toxicity and is known to induce anemia.

Treatment of HCV Infection with Interferon

Interferons (IFNs) are compounds which have been commercially available for the treatment of chronic hepatitis for nearly a decade. IFNs are glycoproteins produced by immune cells in response to viral infection. IFNs inhibit viral replication of many viruses, including HCV, and when used as the sole treatment for hepatitis C infection, IFN supresses serum HCV-RNA to undetectable levels. Additionally, IFN normalizes serum amino transferase levels. Unfortunately, the effects of IFN are temporary and a sustained response occurs in only 8%-9% of patients chronically infected with HCV (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000).

A number of patents disclose HCV treatments using interferon-based therapies. For example, U.S. Pat. No. 5,980,884 to Blatt *et al.* discloses methods for retreatment of patients afflicted with HCV using consensus interferon. U.S. Pat. No. 5,942,223 to Bazer *et al.* discloses an anti-HCV therapy using ovine or bovine interferon-tau. U.S. Pat. No. 5,928,636 to Alber *et al.* discloses the combination therapy of interleukin-12 and interferon alpha for the treatment of infectious diseases including HCV. U.S. Pat. No. 5,908,621 to Glue *et al.* discloses the use of polyethylene glycol modified interferon for the treatment of HCV. U.S. Pat. No. 5,849,696 to Chretien *et al.* discloses the use of thymosins, alone or in combination with interferon, for treating HCV. U.S. Pat. No. 5,830,455 to Valtuena *et al.* discloses a combination HCV therapy employing interferon and a free radical scavenger. U.S. Pat. No. 5,738,845 to Imakawa dislcoses the use of human interferon tau proteins for treating HCV. Other interferon-based treatments for HCV are disclosed in U.S. Pat. No. 5,676,942 to Testa *et al.*, U.S. Pat. No. 5,372,808 to Blatt *et al.*, and U.S. Pat. No. 5,849,696.

Combination of Interferon and Ribavirin

The combination of IFN and Ribavirin for the treatment of HCV infection has been reported to be effective in the treatment of IFN naïve patients. (Battaglia, A.M. *et al.*, *Ann. Pharmacother.* 34:487-494, 2000). Results are promising for this combination treatment both before hepatitis develops or when histological disease is present (Berenguer, M. *et al. Antivir. Ther.* 3(Suppl. 3):125-136, 1998). Side effects of combination therapy include hemolysis, flulike symptoms, anemia, and fatigue. (Gary L. Davis. *Gastroenterology* 118:S104-S114, 2000).

Additional Published Treatments of HCV Infections

A number of HCV treatments are reviewed by Bymock *et al.* in *Antiviral Chemistry &*

Chemotherapy, 11:2; 79-95 (2000).

Several substrate-based NS3 protease inhibitors have been identified in the literature, in which the scissile amide bond of a cleaved substrate is replaced by an electrophile, which interacts with the catalytic serine. Attwood *et al.* (1998) *Antiviral peptide derivatives*, 98/22496; Attwood *et al.* (1999), *Antiviral Chemistry and Chemotherapy* 10.259-273; Attwood *et al.* (1999) *Preparation and use of amino acid derivatives as anti-viral agents,* German Patent Pub. DE 19914474; Tung *et al.* (1998) *Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease*, WO 98/17679. The reported inhibitors terminate in an electrophile such as a boronic acid or phosphonate. Llinas-Brunet *et al.* (1999) *Hepatitis C inhibitor peptide analogues,* WO 99/07734. Two classes of electrophile-based inhibitors have been described, alphaketoamides and hydrazinoureas.

The literature has also described a number of non-substrate-based inhibitors. For example, evaluation of the inhibitory effects of 2,4,6-trihydroxy-3-nitro-benzamide derivatives against HCV protease and other serine proteases has been reported. Sudo, K. *et al.*, (1997) *Biochemical and Biophysical Research Communications*, 238:643-647; Sudo, K. *et al.* (1998) *Antiviral Chemistry and Chemotherapy* 9:186. Using a reverse-phase HPLC assay, the two most potent compounds identified were RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a *para*-phenoxyphenyl group.

Thiazolidine derivatives have been identified as micromolar inhibitors, using a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate. Sudo, K. *et al.* (1996) *Antiviral Research* 32:9-18. Compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, was the most potent against the isolated enzyme. Two other active examples were RD4 6205 and RD4 6193.

Other literature reports screening of a relatively small library using an ELISA assay and the identification of three compounds as potent inhibitors, a thiazolidine and two benzanilides. Kakiuchi N. *et al. J. EBS Letters* 421:217-220; Takeshita N. *et al.*, *Analytical Biochemistry* 247:242-246, 1997. Several U.S. patents disclose protease inhibitors for the treatment of HCV. For example, U.S. Patent No. 6,004,933 to Spruce *et al.* discloses a class of cysteine protease inhibitors for inhibiting HCV endopeptidase 2. U.S. Pat. No. 5,990,276 to Zhang *et al.* discloses synthetic inhibitors of hepatitis C virus NS3 protease. The inhibitor is a subsequence of a substrate of the NS3 protease or a substrate of the NS4A cofactor. The use of restriction

enzymes to treat HCV is disclosed in U.S. Pat. No. 5,538,865 to Reyes *et al.*

Isolated from the fermentation culture broth of *Streptomyces* sp., Sch 68631, a phenanthrenequinone, possessed micromolar activity against HCV protease in a SDS-PAGE and autoradiography assay. Chu M. *et al.*, *Tetrahedron Letters* 37:7229-7232, 1996. In another example by the same authors, Sch 351633, isolated from the fungus *Penicillium griscofuluum,* demonstrated micromolar activity in a scintillation proximity assay. Chu M. *et al.*, *Bioorganic and Medicinal Chemistry Letters* 9:1949-1952. Nanomolar potency against the HCV NS3 protease enzyme has been achieved by the design of selective inhibitors based on the macromolecule eglin c. Eglin c, isolated from leech, is a potent inhibitor of several serine proteases such as S. griseus proteases A and B, α-chymotrypsin, chymase and subtilisin. Qasim M.A. *et al.*, *Biochemistry* 36:1598-1607, 1997.

HCV helicase inhibitors have also been reported. U.S. Pat. No. 5,633,358 to Diana G.D. *et al.*; PCT Pub. No. WO 97/36554 of Diana G.D. *et al.*. There are a few reports of HCV polymerase inhibitors: some nucleotide analogues, gliotoxin, and the natural product cerulenin. Ferrari R. *et al.*, *Journal of Virology* 73:1649-1654, 1999; Lohmann V. *et al.*, *Virology* 249:108-118, 1998.

Antisense phosphorothioate oligodeoxynucleotides complementary to sequence stretches in the 5' non-coding region of the HCV, are reported as efficient inhibitors of HCV gene expression in *in vitro* translation and IIcpG2 IICV-luciferase cell culture systems. Alt M. *et al.*, *Hepatology* 22:707-717, 1995. Recent work has demonstrated that nucleotides 326-348 comprising the 3' end of the NCR and nucleotides 371-388 located in the core coding region of the HCV RNA are effective targets for antisense-mediated inhibition of viral translation. Alt M. *et al.*, *Archives of Virology* 142:589-599, 1997. U.S. Pat. No. 6,001,990 to Wands *et al.* discloses oligonucleotides for inhibiting the replication of HCV. PCT application WO 99/29350 discloses compositions and methods of treatment for hepatitis C infection comprising the administration of antisense oligonucleotides which are complementary and hybridizable to HCV-RNA. U.S. Pat. No. 5,922,857 to Han *et al.* disclose nucleic acids corresponding to the sequence of the pestivirus homology box IV area for controlling the translation of HCV. Antisense oligonucleotides as therapeutic agents have been recently reviewed. Galderisi U. *et al.*, *Journal of Cellular Physiology* 181:251-257, 1999.

Other compounds have been reported as inhibitors of IRES-dependent translation in

HCV. Japanese Patent Pub. JP-08268890 of Ikeda N *et al.*; Japanese Patent Pub. JP-10101591 of Kai, Y. *et al.* Nuclease-resistant ribozymes have been targeted at the IRES and recently reported as inhibitors in an HCV-poliovirus chimera plaque assay. Maccjak D.J. *et al.*, *Hepatology 30* abstract 995, 1999. The use of ribozymes to treat HCV is also disclosed in U.S. Pat. No. 6,043,077 to Barber *et al.*, and U.S. Pat. Nos. 5,869,253 and 5,610,054 to Draper *et al.*

Other patents disclose the use of immune system potentiating compounds for the treatment of HCV. For example, U.S. Pat. No. 6,001,799 to Chretien *et al.* discloses a method of treating hepatitis C in non-responders to interferon treatment by administering an immune system potentiating dose of thymosin or a thymosin fragment. U.S. Pat. Nos. 5,972,347 to Eder *et al.* and 5,969,109 to Bona *et al.* disclose antibody-based treatments for treating HCV.

U.S. Patent No. 6,034,134 to Gold *et al.* discloses certain NMDA receptor agonists having immunodulatory, antimalarial, anti-Borna virus, and anti-Hepatitis C activities. The disclosed NMDA receptor agonists belong to a family of 1-amino-alkylcyclohexanes. U.S. Patent No. 9. 6,030,960 to Morris-Natschke *et al.* discloses the use of certain alkyl lipids to inhibit the production of hepatitis-induced antigens, including those produced by the HCV virus. U.S. Pat. No. 5,922,757 to Chojkier *et al.* discloses the use of vitamin E and other antioxidants to treat hepatic disorders including HCV. U.S. Pat. No. 5,858,389 to Elsherbi *et al.* discloses the use of squalene for treating hepatitis C. U.S. Pat. No. 5,849,800 to Smith et al discloses the use of amantadine for treatment of Hepatitis C. U.S. Pat. No. 5,846,964 to Ozeki *et al.* discloses the use of bile acids for treating HCV. U.S. Pat. No. 5,491,135 to Blough *et al.* discloses the use of N-(phosphonoacetyl)-L-aspartic acid to treat flaviviruses such as HCV.

Other compounds proposed for treating HCV include plant extracts (U.S. Pat. No. 5,837,257 to Tsai *et al.*, U.S. Pat. No. 5,725,859 to Omer *et al.*, and U.S. Pat. No. 6,056,961), piperidenes (U.S. Pat. No. 5,830,905 to Diana *et al.*), benzenedicarboxamides (U.S. Pat. No. 5,633,388 to Diana *et al.*), polyadenylic acid derivatives (U.S. Pat. No. 5,496,546 to Wang *et al.*), 2',3'-dideoxyinosine (U.S. Pat. No. 5,026,687 to Yarchoan *et al.*), benzimidazoles (U.S. Pat. No. 5,891,874 to Colacino *et al.*).

In light of the fact that the hepatitis C virus has reached epidemic levels worldwide, and has tragic effects on the infected patient, there remains a strong need to provide new effective pharmaceutical agents to treat hepatitis C that has low toxicity to the host.

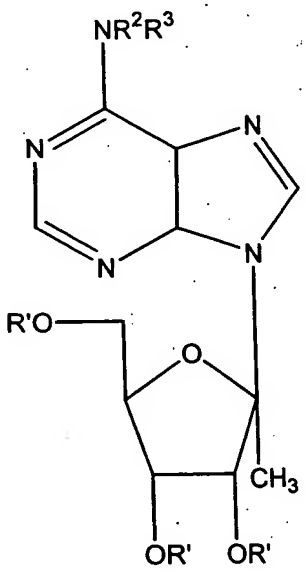
Therefore, it is an object of the present invention to provide a method and composition

for the treatment of a host infected with hepatitis C.

SUMMARY OF THE INVENTION

Methods and compositions for the treatment of hepatitis C infection are described that include an effective hepatitis C treatment amount of a β-D- or β-L-nucleoside of the Formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XII), (XIII), or (XIV), or a pharmaceutically acceptable salt or prodrug thereof.

In a first principal embodiment, a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



I

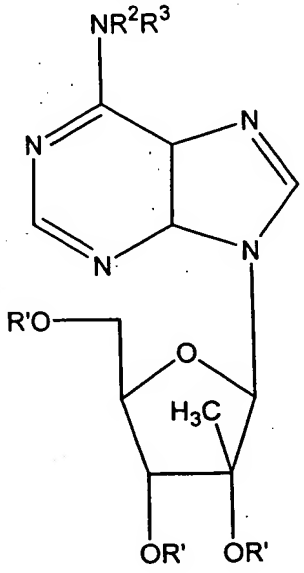
wherein:

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^2 and R^3 are independently hydrogen, acyl (including lower acyl), or alkyl (including

but not limited to methyl, ethyl, propyl, and cyclopropyl).

In a second principal embodiment, a compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



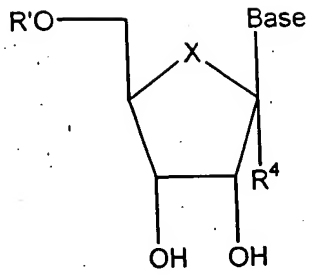
II

wherein:

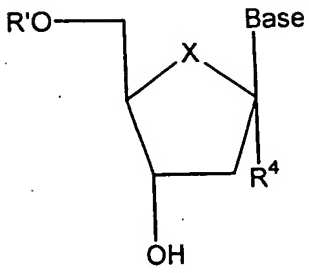
R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^2 and R^3 are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl, and cyclopropyl).

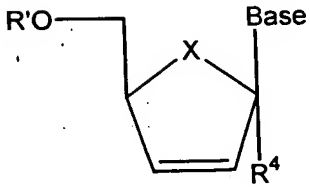
In a third principal embodiment, a compound selected from Formulas III, IV, and V, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



III



IV



V

wherein:

Base is a purine or pyrimidine base as defined herein;

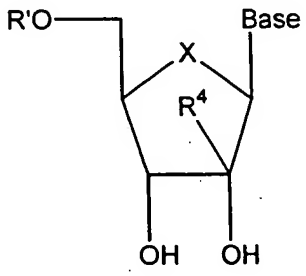
R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate;

R^4 is hydrogen, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, 2-Br-ethyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl),

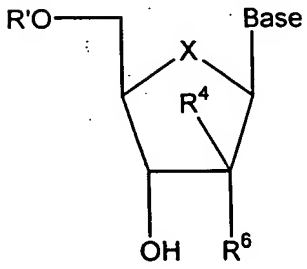
-O(lower alkyl), -O(alkenyl), CF_3, halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

X is O, S, SO_2, or CH_2.

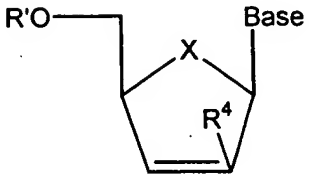
In a fourth principal embodiment, a compound of Formulas VI, VII, and VIII, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



VI



VII



VIII

wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in

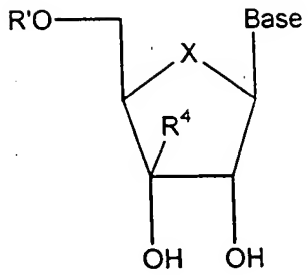
the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^4 is hydrogen, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

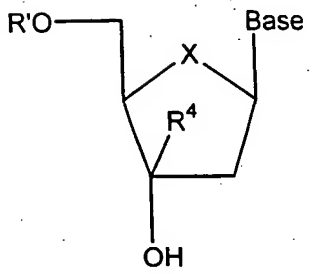
R^6 is hydrogen, OR^1, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

X is O, S, SO_2, or CH_2.

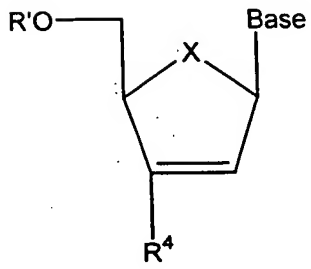
In a fifth principal embodiment a compound selected from Formulas IX, X, and XI, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



IX



X



XI

wherein:

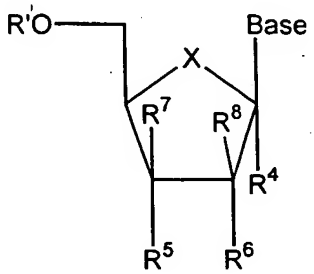
Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^4 is hydrogen, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

X is O, S, SO_2, or CH_2.

In a sixth principal embodiment the invention provides a compound of Formula XII, or a pharmaceutically acceptable salt or prodrug thereof:



XII

wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

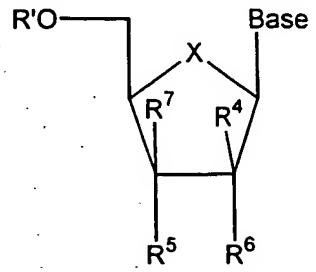
R^4 is hydrogen, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

R^5 and R^6 are independently hydrogen, OR^1, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

R^7 and R^8 are independently H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and

X is O, S, SO_2, or CH_2.

In a seventh principal embodiment the invention provides a compound of Formula XIII, or a pharmaceutically acceptable salt or prodrug thereof:



XIII

wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

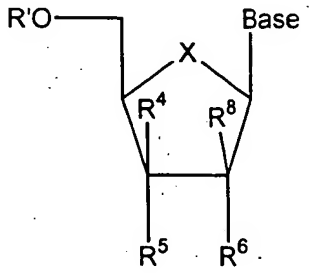
R^4 is hydrogen, hydroxy, alkyl (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

R^5 and R^6 are independently hydrogen, OR^1, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

R^7 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and

X is O, S, SO_2, or CH_2.

In an eighth principal embodiment the invention provides a compound of Formula XIV, or a pharmaceutically acceptable salt or prodrug thereof:



XIV

wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^4 is hydrogen, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

R^5 and R^6 are independently hydrogen, OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino;

R^8 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and

X is O, S, SO_2, or CH_2.

The β-D- and β-L-nucleosides of this invention belong to a class of anti-HCV agents that inhibit HCV polymerase activity. Nucleosides can be screened for their ability to inhibit HCV polymerase activity *in vitro* according to screening methods set forth more particularly herein.

One can readily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay.

In one embodiment the efficacy of the anti-HCV compound is measured according to the concentration of compound necessary to reduce the plaque number of the virus *in vitro*, according to methods set forth more particularly herein, by 50% (i.e. the compound's EC_{50}). In preferred embodiments the compound exhibits an EC_{50} of less than 25, 15, 10, 5, or 1 micromolar.

In another embodiment, the active compound can be administered in combination or alternation with another anti-HCV agent. In combination therapy, an effective dosage of two or more agents are administered together, whereas during alternation therapy an effective dosage of each agent is administered serially. The dosages will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens and schedules should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include:

(1) an interferon and/or ribavirin (Battaglia, A.M. *et al.*, Ann. Pharmacother. 34:487-494, 2000); Berenguer, M. *et al.* Antivir. Ther. 3(Suppl. 3):125-136, 1998);

(2) Substrate-based NS3 protease inhibitors (Attwood *et al.*, *Antiviral peptide derivatives*, PCT WO 98/22496, 1998; Attwood *et al.*, *Antiviral Chemistry and Chemotherapy* 10.259-273, 1999; Attwood *et al.*, *Preparation and use of amino acid derivatives as anti-viral agents,* German Patent Pub. DE 19914474; Tung *et al. Inhibitors of serine proteases, particularly hepatitis C virus NS3 protease*, PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate. Llinas-Brunet et al, *Hepatitis C inhibitor peptide analogues,* PCT WO 99/07734.

(3) Non-substrate-based inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives(Sudo K. *et al.*, *Biochemical and Biophysical Research Communications,* 238:643-647, 1997; Sudo K. *et al. Antiviral Chemistry and Chemotherapy* 9:186, 1998), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter

processing a *para*-phenoxyphenyl group;

(4) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo K. *et al., Antiviral Research* 32:9-18, 1996), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;

(5) Thiazolidines and benzanilides identified in Kakiuchi N. *et al. J. EBS Letters* 421:217-220; Takeshita N. *et al. Analytical Biochemistry* 247:242-246, 1997;

(6) A phenan-threnequinone possessing activity against HCV protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of *Streptomyces* sp., Sch 68631 (Chu M. *et al., Tetrahedron Letters* 37:7229-7232, 1996), and Sch 351633, isolated from the fungus *Penicillium griscofuluum,* which demonstrates activity in a scintillation proximity assay (Chu M. *et al., Bioorganic and Medicinal Chemistry Letters* 9:1949-1952);

(7) Selective NS3 inhibitors based on the macromolecule elgin c, isolated from leech (Qasim M.A. *et al., Biochemistry* 36:1598-1607, 1997);

(8) HCV helicase inhibitors (Diana G.D. *et al., Compounds, compositions and methods for treatment of hepatitis C,* U.S. Pat. No. 5,633,358; Diana G.D. *et al., Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C,* PCT WO 97/36554);

(9) HCV polymerase inhibitors such as nucleotide analogues, gliotoxin (Ferrari R. *et al. Journal of Virology* 73:1649-1654, 1999), and the natural product cerulenin (Lohmann V. *et al., Virology* 249:108-118, 1998);

(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' non-coding region (NCR) of the HCV (Alt M. *et al., Hepatology* 22:707-717, 1995), or nucleotides 326-348 comprising the 3' end of the NCR and nucleotides 371-388 located in the core coding region of the IICV RNA (Alt M. *et al., Archives of Virology* 142:589-599, 1997; Galderisi U. *et al., Journal of Cellular Physiology* 181:251-257, 1999);

(11) Inhibitors of IRES-dependent translation (Ikeda N *et al., Agent for the prevention and treatment of hepatitis C,* Japanese Patent Pub. JP-08268890; Kai Y. *et al. Prevention and treatment of viral diseases,* Japanese Patent Pub. JP-10101591);

(12) Nuclease-resistant ribozymes. (Maccjak D.J. *et al., Hepatology 30* abstract 995, 1999); and

(13) Other miscellaneous compounds including 1-amino-alkylcyclohexanes (U.S. Patent No. 6,034,134 to Gold *et al.*), alkyl lipids (U.S. Pat. No. 5,922,757 to Chojkier *et al.*), vitamin E and other antioxidants (U.S. Pat. No. 5,922,757 to Chojkier *et al.*), squalene, amantadine, bile acids (U.S. Pat. No. 5,846,964 to Ozeki *et al.*), N-(phosphonoacetyl)-L-aspartic acid, (U.S. Pat. No. 5,830,905 to Diana *et al.*), benzenedicarboxamides (U.S. Pat. No. 5,633,388 to Diana *et al.*), polyadenylic acid derivatives (U.S. Pat. No. 5,496,546 to Wang *et al.*), 2',3'-dideoxyinosine (U.S. Pat. No. 5,026,687 to Yarchoan *et al.*), and benzimidazoles (U.S. Pat. No. 5,891,874 to Colacino *et al.*).

DETAILED DESCRIPTION OF THE INVENTION

The invention as disclosed herein is a compound, method and composition for the treatment of hepatitis C in humans or other host animals, that includes administering an effective HCV treatment amount of a β-D- or β-L-nucleoside as described herein or a pharmaceutically acceptable salt or prodrug thereof, optionally in a pharmaceutically acceptable carrier. The compounds of this invention either possess antiviral (i.e., anti-HCV) activity, or are metabolized to a compound that exhibits such activity.

In summary, the present invention includes the following features:

(a) β-D- and β-L-nucleosides, as described herein, and pharmaceutically acceptable salts and prodrugs thereof;

(b) β-D- and β-L-nucleosides as described herein, and pharmaceutically acceptable salts and prodrugs thereof for use in the treatment or prophylaxis of an HCV infection, especially in individuals diagnosed as having an HCV infection or being at risk for becoming infected by HCV;

(c) use of these β-D- and β-L-nucleosides, and pharmaceutically acceptable salts and prodrugs thereof in the manufacture of a medicament for treatment of an HCV infection;

(d) pharmaceutical formulations comprising the β-D- or β-L-nucleosides or pharmaceutically acceptable salts or prodrugs thereof together with a pharmaceutically acceptable carrier or diluent;

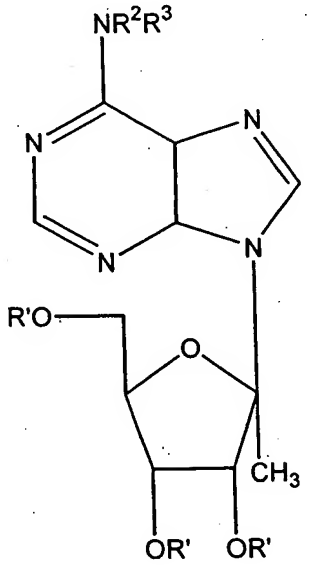
(e) β-D- and β-L-nucleosides as described herein substantially in the absence of enantiomers of the described nucleoside, or substantially isolated from other chemical entities;

(f) processes for the preparation of β-D- and β-L-nucleosides, as described in more detail below; and

(g) processes for the preparation of β-D- and β-L-nucleosides substantially in the absence of enantiomers of the described nucleoside, or substantially isolated from other chemical entities.

I. Active Compound, and Physiologically Acceptable Salts and Prodrugs Thereof

In a first principal embodiment, a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



I

wherein:

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

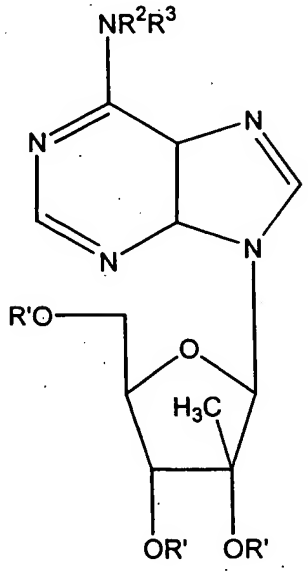
R^2 and R^3 are independently hydrogen, acyl (including lower acyl), or alkyl (including but not limited to methyl, ethyl, propyl, and cyclopropyl).

In a preferred subembodiment, a compound of Formula I, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

R^1 is independently H or phosphate (preferably H); and

R^2 and R^3 are hydrogen.

In a second principal embodiment, a compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



II

wherein:

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^2 and R^3 are independently hydrogen, acyl (including lower acyl), or alkyl (including

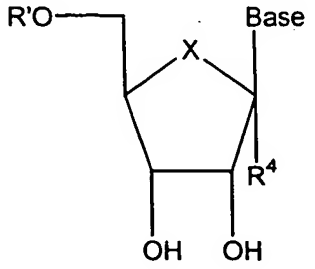
but not limited to methyl, ethyl, propyl, and cyclopropyl).

In a preferred subembodiment, a compound of Formula II, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

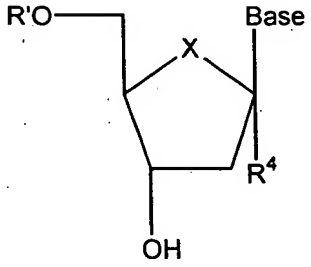
R^1 is independently H or phosphate (preferably H); and

R^2 and R^3 are hydrogen.

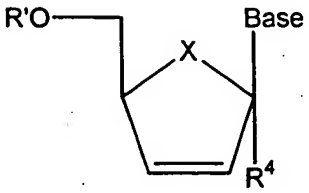
In a third principal embodiment, a compound selected from Formulas III, IV, and V, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



III



IV



V

wherein:

Base is a purine or pyrimidine base as defined herein;

wherein:

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl);

sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate;

R^4 is hydrogen, hydroxy, alkyl, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

X is O, S, SO_2, or CH_2.

In a first preferred subembodiment, a compound of Formula III, IV, or V, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is H or phosphate;

R^4 is alkyl; and

X is O, S, SO_2, or CH_2.

In a second preferred subembodiment, a compound of Formula III, IV, or V, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is H;

R^4 is alkyl; and

X is O, S, SO_2, or CH_2.

In a third preferred subembodiment, a compound of Formula III, IV, or V, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

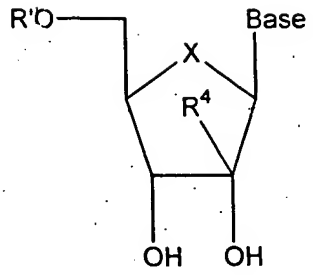
Base is a purine or pyrimidine base as defined herein;

R^1 is H or phosphate;

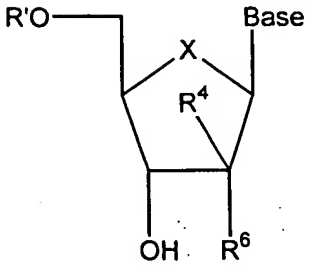
R^4 is alkyl; and

X is O.

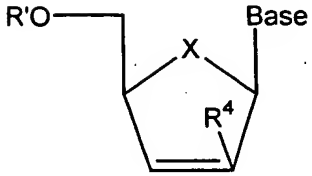
In a fourth principal embodiment, a compound of Formulas VI, VII, and VIII, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



VI



VII



VIII

wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl; alkyl; sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^4 is hydrogen, hydroxy, alkyl, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

X is O, S, SO_2, or CH_2.

In a first preferred subembodiment, a compound of Formula VI, VII, or VIII, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is H or phosphate;

R^4 is alkyl; and

X is O, S, SO_2, or CH_2.

In a second preferred subembodiment, a compound of Formula VI, VII, or VIII, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is H;

R^4 is alkyl; and

X is O, S, SO_2, or CH_2.

In a third preferred subembodiment, a compound of Formula VI, VII, or VIII, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

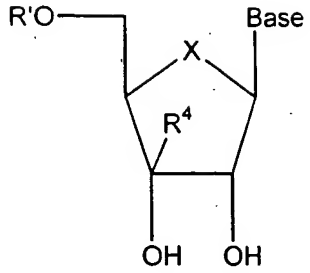
Base is a purine or pyrimidine base as defined herein;

R^1 is H or phosphate;

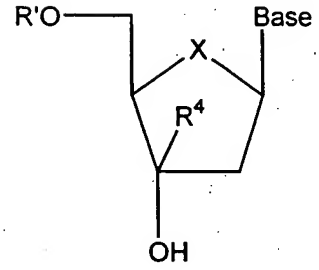
R^4 is alkyl; and

X is O.

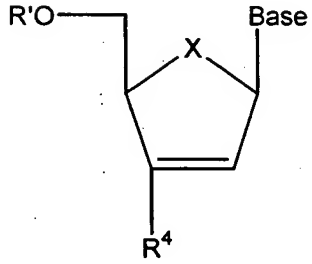
In a fifth principal embodiment a compound selected from Formulas IX, X, and XI, or a pharmaceutically acceptable salt or prodrug thereof, is provided:



IX



X



XI

wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^4 is hydrogen, hydroxy, alkyl, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

X is O, S, SO_2, or CH_2.

In a first preferred subembodiment, a compound of Formula IX, X, or XI, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is H or phosphate;

R^4 is alkyl; and

X is O, S, SO_2, or CH_2.

In a second preferred subembodiment, a compound of Formula IX, X, or XI, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is H;

R^4 is alkyl; and

X is O, S, SO_2, or CH_2.

In a third preferred subembodiment, a compound of Formula IX, X, or XI, or a pharmaceutically acceptable salt or prodrug thereof, is provided wherein:

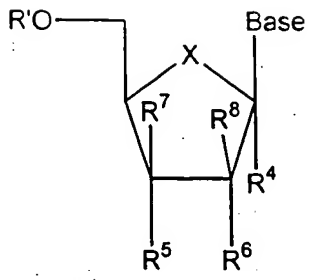
Base is a purine or pyrimidine base as defined herein;

R^1 is H or phosphate;

R^4 is alkyl; and

X is O.

In a sixth principal embodiment the invention provides a compound of Formula XII, or a pharmaceutically acceptable salt or prodrug thereof:



XII

wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^4 is hydrogen, hydroxy, alkyl, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

R^5 and R^6 are independently hydrogen, OR^1, hydroxy, alkyl, azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

R^7 and R^8 are independently H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and

X is O, S, SO_2, or CH_2.

In a first preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including

lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are OR^1, alkyl, alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 and R^8 are independently H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O, S, SO_2, or CH_2.

In a second preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl, alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are OR^1; (5) R^7 and R^8 are independently H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O, S, SO_2, or CH_2.

In a third preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is

independently H or phosphate; (3) R^4 is alkyl, alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are OR^1, alkyl, alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 and R^8 are H; and (6) X is O, S, SO_2, or CH_2.

In a fourth preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl, alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are OR^1, alkyl, alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 and R^8 are independently H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O.

In a fifth preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are OR^1; (5) R^7 and R^8 are independently H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O, S, SO_2, or CH_2.

In a sixth preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 and R^8 are H; and (6) X is O, S, SO_2, or CH_2.

In a seventh preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 and R^8 are independently H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O.

In a eighth preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with

one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are OR^1; (5) R^7 and R^8 are hydrogen; and (6) X is O, S, SO_2, or CH_2.

In a ninth preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are OR^1; (5) R^7 and R^8 are independently H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O.

In a tenth preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino;

(4) R^5 and R^6 are OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 and R^8 are hydrogen; and (6) X is O.

In an eleventh preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are OR^1; (5) R^7 and R^8 are hydrogen; and (6) X is O, S, SO_2, or CH_2.

In a twelfth preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are OR^1; (5) R^7 and R^8 are hydrogen; and (6) X is O, S, SO_2, or CH_2.

In a thirteenth preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are OR^1; (5) R^7 and R^8 are independently H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O.

In a fourteenth preferred subembodiment, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 and R^8 are hydrogen; and (6) X is O.

In even more preferred subembodiments, a compound of Formula XII, or its pharmaceutically acceptable salt or prodrug, is provided in which:

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is O;

(1) Base is guanine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is O;

(1) Base is cytosine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is O;

(1) Base is thymine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is O;

(1) Base is uracil; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is phosphate; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is ethyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is propyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is butyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is O;

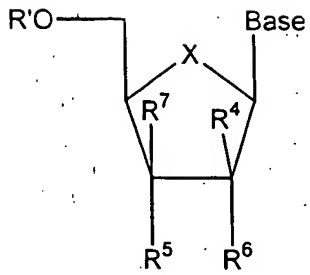
(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 is hydroxy and R^6 is hydrogen; (5) R^7 and R^8 are hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is S;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is SO_2;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 and R^8 are hydrogen; and (6) X is CH_2;

In a seventh principal embodiment the invention provides a compound of Formula XIII, or a pharmaceutically acceptable salt or prodrug thereof:



XIII

wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate;

R^4 is hydrogen, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

R^5 and R^6 are independently hydrogen, OR^1, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), chlorine, bromine, iodine, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$;

R^7 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and

X is O, S, SO_2, or CH_2.

In a first preferred subembodiment, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid;

a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently hydrogen, OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 is H; and (6) X is O, S, SO_2, or CH_2.

In a second preferred subembodiment, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are OR^1; (5) R^7 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O, S, SO_2, or CH_2.

In a third preferred subembodiment, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino;

(4) R^5 and R^6 are independently hydrogen, OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O.

In a fourth preferred subembodiment, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently OR^1; (5) R^7 is H; and (6) X is O, S, SO_2, or CH_2.

In a fifth preferred subembodiment, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently OR^1; (5) R^7 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O.

In a sixth preferred subembodiment, a compound of Formula XIII, or its

pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently hydrogen, OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 is H; and (6) X is O.

In a seventh preferred subembodiment, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently OR^1; (5) R^7 is H; and (6) X is O.

In an eighth preferred subembodiment, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are independently hydrogen, OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^7 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and

(6) X is O, S, SO_2, or CH_2.

In a ninth preferred subembodiment, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are OR^1; (5) R^7 is H; and (6) X is O, S, SO_2, or CH_2.

In a tenth preferred subembodiment, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are OR^1; (5) R^7 is H; and (6) X is O, S, SO_2, or CH_2.

In even more preferred subembodiments, a compound of Formula XIII, or its pharmaceutically acceptable salt or prodrug, is provided in which:

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is O;

(1) Base is guanine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is O;

(1) Base is cytosine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is O;

(1) Base is thymine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is O;

(1) Base is uracil; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is phosphate; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is ethyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is propyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is O;

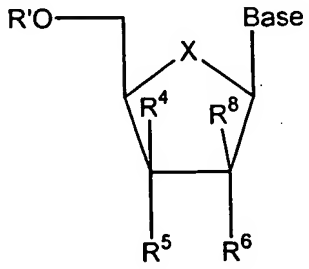
(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is butyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is S;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is SO_2; or

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^7 is hydrogen; and (6) X is CH_2.

In an eighth principal embodiment the invention provides a compound of Formula XIV, or a pharmaceutically acceptable salt or prodrug thereof:



XIV

wherein:

Base is a purine or pyrimidine base as defined herein;

R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; and

R^4 is hydrogen, hydroxy, alky (including lower alkyl), azido, cyano, alkenyl, alkynyl, Br-vinyl, -C(O)O(alkyl), -C(O)O(lower alkyl), -O(acyl), -O(lower acyl), -O(alkyl), -O(lower alkyl), -O(alkenyl), halogen, NO_2, NH_2, -NH(lower alkyl), -NH(acyl), -N(lower alkyl)$_2$, -N(acyl)$_2$; and

R^5 and R^6 are independently hydrogen, OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino;

R^8 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and

X is O, S, SO_2, or CH_2.

In a first preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are independently hydrogen, OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^8 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O, S, SO_2, or CH_2.

In a second preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently OR^1; (5) R^8 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O, S, SO_2, or CH_2.

In a third preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including

monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently hydrogen, OR^1, alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^8 is H; and (6) X is O, S, SO_2, or CH_2.

In a fourth preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently hydrogen, OR^1, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^8 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O.

In a fifth preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and

benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently OR^1; (5) R^8 is H; and (6) X is O, S, SO_2, or CH_2.

In a sixth preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are independently OR^1; (5) R^8 is H, alkyl (including lower alkyl), chlorine, bromine, or iodine; and (6) X is O.

In a seventh preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H; phosphate (including monophosphate, diphosphate, triphosphate, or a stabilized phosphate prodrug); acyl (including lower acyl); alkyl (including lower alkyl); sulfonate ester including alkyl or arylalkyl sulfonyl including methanesulfonyl and benzyl, wherein the phenyl group is optionally substituted with one or more substituents as described in the definition of aryl given herein; a lipid, including a phospholipid; an amino acid; a carbohydrate; a peptide; a cholesterol; or other pharmaceutically acceptable leaving group which when administered *in vivo* is capable of providing a compound wherein R^1 is independently H or phosphate; (3) R^4 is alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or

di(lower)alkylamino; (4) R^5 and R^6 are independently hydrogen, OR^1, alkyl (including lower alkyl), alkenyl, alkynyl, Br-vinyl, O-alkenyl, chlorine, bromine, iodine, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (5) R^8 is H; and (6) X is O.

In an eighth preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alky (including lower alkyl), alkenyl, alkynyl, Br-vinyl, hydroxy, O-alkyl, O-alkenyl, halogen, NO_2, amino, loweralkylamino, or di(lower)alkylamino; (4) R^5 and R^6 are OR^1; (5) R^8 is H; and (6) X is O, S, SO_2, or CH_2.

In a ninth preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are independently OR^1; (5) R^8 is H; and (6) X is O, S, SO_2, or CH_2.

In a tenth preferred subembodiment, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which: (1) Base is a purine or pyrimidine base as defined herein; (2) R^1 is independently H or phosphate; (3) R^4 is alkyl; (4) R^5 and R^6 are OR^1; (5) R^8 is H; and (6) X is O.

In even more preferred subembodiments, a compound of Formula XIV, or its pharmaceutically acceptable salt or prodrug, is provided in which:

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is O;

(1) Base is guanine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is O;

(1) Base is cytosine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is O;

(1) Base is thymine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is O;

(1) Base is uracil; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is phosphate; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is ethyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is propyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is butyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is O;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is S;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is SO_2;

(1) Base is adenine; (2) R^1 is hydrogen; (3) R^4 is methyl; (4) R^5 and R^6 are hydroxy; (5) R^8 is hydrogen; and (6) X is CH_2;

The β-D- and β-L-nucleosides of this invention belong to a class of anti-HCV agents that inhibit HCV polymerase activity. Nucleosides can be screened for their ability to inhibit HCV polymerase activity *in vitro* according to screening methods set forth more particularly herein. One can readily determine the spectrum of activity by evaluating the compound in the assays described herein or with another confirmatory assay.

In one embodiment the efficacy of the anti-HCV compound is measured according to the concentration of compound necessary to reduce the plaque number of the virus *in vitro*, according to methods set forth more particularly herein, by 50% (i.e. the compound's EC_{50}). In preferred embodiments the compound exhibits an EC_{50} of less than 15 or 10 micromolar, when measured according to the polymerase assay described in Ferrari *et al., Jnl. of Vir.*, 73:1649-1654, 1999; Ishii *et al., Hepatology*, 29:1227-1235,1999; Lohmann *et al., Jnl. of Bio. Chem.*, 274:10807-10815, 1999; or Yamashita *et al, Jnl. of Bio. Chem.*, 273:15479-15486, 1998.

The active compound can be administered as any salt or prodrug that upon administration to the recipient is capable of providing directly or indirectly the parent compound, or that exhibits activity itself. Nonlimiting examples are the pharmaceutically acceptable salts (alternatively referred to as "physiologically acceptable salts"), and a compound which has been alkylated or acylated at the 5'-position or on the purine or pyrimidine base (a type of "pharmaceutically acceptable prodrug"). Further, the modifications can affect the biological activity of the compound, in some cases increasing the activity over the parent compound. This

can easily be assessed by preparing the salt or prodrug and testing its antiviral activity according to the methods described herein, or other methods known to those skilled in the art.

The term alkyl, as used herein, unless otherwise specified, refers to a saturated straight, branched, or cyclic, primary, secondary, or tertiary hydrocarbon of C_1 to C_{10}, and specifically includes methyl, ethyl, propyl, isopropyl, cyclopropyl, butyl, isobutyl, *t*-butyl, pentyl, cyclopentyl, isopentyl, neopentyl, hexyl, isohexyl, cyclohexyl, cyclohexylmethyl, 3-methylpentyl, 2,2-dimethylbutyl, and 2,3-dimethylbutyl. The term includes both substituted and unsubstituted alkyl groups. Moieties with which the alkyl group can be substituted are selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991, hereby incorporated by reference.

The term lower alkyl, as used herein, and unless otherwise specified, refers to a C_1 to C_4 saturated straight, branched, or if appropriate, a cyclic (for example, cyclopropyl) alkyl group, including both substituted and unsubstituted forms. Unless otherwise specifically stated in this application, when alkyl is a suitable moiety, lower alkyl is preferred. Similarly, when alkyl or lower alkyl is a suitable moiety, unsubstituted alkyl or lower alkyl is preferred.

The term alkylamino or arylamino refers to an amino group that has one or two alkyl or aryl substituents, respectively.

The term "protected" as used herein and unless otherwise defined refers to a group that is added to an oxygen, nitrogen, or phosphorus atom to prevent its further reaction or for other purposes. A wide variety of oxygen and nitrogen protecting groups are known to those skilled in the art of organic synthesis.

The term aryl, as used herein, and unless otherwise specified, refers to phenyl, biphenyl, or naphthyl, and preferably phenyl. The term includes both substituted and unsubstituted moieties. The aryl group can be substituted with one or more moieties selected from the group consisting of hydroxyl, amino, alkylamino, arylamino, alkoxy, aryloxy, nitro, cyano, sulfonic acid, sulfate, phosphonic acid, phosphate, or phosphonate, either unprotected, or protected as necessary, as known to those skilled in the art, for example, as taught in Greene, *et al.*, Protective Groups in Organic Synthesis, John Wiley and Sons, Second Edition, 1991.

The term alkaryl or alkylaryl refers to an alkyl group with an aryl substituent. The term aralkyl or arylalkyl refers to an aryl group with an alkyl substituent.

The term halo, as used herein, includes chloro, bromo, iodo, and fluoro.

The term purine or pyrimidine base includes, but is not limited to, adenine, N^6-alkylpurines, N^6-acylpurines (wherein acyl is C(O)(alkyl, aryl, alkylaryl, or arylalkyl), N^6-benzylpurine, N^6-halopurine, N^6-vinylpurine, N^6-acetylenic purine, N^6-acyl purine, N^6-hydroxyalkyl purine, N^6-thioalkyl purine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, thymine, cytosine, 5-fluorocytosine, 5-methylcytosine, 6-azapyrimidine, including 6-azacytosine, 2- and/or 4-mercaptopyrmidine, uracil, 5-halouracil, including 5-fluorouracil, C^5-alkylpyrimidines, C^5-benzylpyrimidines, C^5-halopyrimidines, C^5-vinylpyrimidine, C^5-acetylenic pyrimidine, C^5-acyl pyrimidine, C^5-hydroxyalkyl purine, C^5-amidopyrimidine, C^5-cyanopyrimidine, C^5-nitropyrimidine, C^5-aminopyrimidine, N^2-alkylpurines, N^2-alkyl-6-thiopurines, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl. Purine bases include, but are not limited to, guanine, adenine, hypoxanthine, 2,6-diaminopurine, and 6-chloropurine. Functional oxygen and nitrogen groups on the base can be protected as necessary or desired. Suitable protecting groups are well known to those skilled in the art, and include trimethylsilyl, dimethylhexylsilyl, *t*-butyldimethylsilyl, and *t*-butyldiphenylsilyl, trityl, alkyl groups, and acyl groups such as acetyl and propionyl, methanesulfonyl, and p-toluenesulfonyl.

The term acyl refers to a carboxylic acid ester in which the non-carbonyl moiety of the ester group is selected from straight, branched, or cyclic alkyl or lower alkyl, alkoxyalkyl including methoxymethyl, aralkyl including benzyl, aryloxyalkyl such as phenoxymethyl, aryl including phenyl optionally substituted with halogen, C_1 to C_4 alkyl or C_1 to C_4 alkoxy, sulfonate esters such as alkyl or aralkyl sulphonyl including methanesulfonyl, the mono, di or triphosphate ester, trityl or monomethoxytrityl, substituted benzyl, trialkylsilyl (e.g. dimethyl-t-butylsilyl) or diphenylmethylsilyl. Aryl groups in the esters optimally comprise a phenyl group. The term "lower acyl" refers to an acyl group in which the non-carbonyl moiety is lower alkyl.

As used herein, the term "substantially free of" or "substantially in the absence of" refers to a nucleoside composition that includes at least 85 or 90% by weight, preferably 95% to 98 % by weight, and even more preferably 99% to 100% by weight, of the designated enantiomer of that nucleoside. In a preferred embodiment, in the methods and compounds of this invention, the

compounds are substantially free of enantiomers.

Similarly, the term "isolated" refers to a nucleoside composition that includes at least 85 or 90% by weight, preferably 95% to 98 % by weight, and even more preferably 99% to 100% by weight, of the nucleoside, the remainder comprising other chemical species or enantiomers.

The term "independently" is used herein to indicate that the variable which is independently applied varies independently from application to application. Thus, in a compound such as R"XYR", wherein R" is "independently carbon or nitrogen," both R" can be carbon, both R" can be nitrogen, or one R" can be carbon and the other R" nitrogen.

Nucleotide Prodrug Formulations

Any of the nucleosides described herein can be administered as a nucleotide prodrug to increase the activity, bioavailability, stability or otherwise alter the properties of the nucleoside. A number of nucleotide prodrug ligands are known. In general, alkylation, acylation or other lipophilic modification of the mono, di or triphosphate of the nucleoside will increase the stability of the nucleotide. Examples of substituent groups that can replace one or more hydrogens on the phosphate moiety are alkyl, aryl, steroids, carbohydrates, including sugars, 1,2-diacylglycerol and alcohols. Many are described in R. Jones and N. Bischofberger, *Antiviral Research*, **27** (1995) 1-17. Any of these can be used in combination with the disclosed nucleosides to achieve a desired effect.

The active nucleoside can also be provided as a 5'-phosphoether lipid or a 5'-ether lipid, as disclosed in the following references, which are incorporated by reference herein: Kucera, L.S., N. Iyer, E. Leake, A. Raben, Modest E.K., D.L.W., and C. Piantadosi. 1990. "Novel membrane-interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation." *AIDS Res. Hum. Retro Viruses*. **6**:491-501; Piantadosi, C., J. Marasco C.J., S.L. Morris-Natschke, K.L. Meyer, F. Gumus, J.R. Surles, K.S. Ishaq, L.S. Kucera, N. Iyer, C.A. Wallen, S. Piantadosi, and E.J. Modest. 1991. "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV activity." *J. Med. Chem.* **34**:1408.1414; Hosteller, K.Y., D.D. Richman, D.A. Carson, L.M. Stuhmiller, G.M. T. van Wijk, and H. van den Bosch. 1992. "Greatly enhanced inhibition of human immunodeficiency virus type 1 replication in CEM and HT4-6C cells by 3'-deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 3,-deoxythymidine." *Antimicrob. Agents Chemother.* **36**:2025.2029; Hosetler, K.Y., L.M. Stuhmiller, H.B. Lenting, H. van den Bosch, and D.D. Richman, 1990. "Synthesis

and antiretroviral activity of phospholipid analogs of azidothymidine and other antiviral nucleosides." *J. Biol. Chem.* 265:61127.

Nonlimiting examples of U.S. patents that disclose suitable lipophilic substituents that can be covalently incorporated into the nucleoside, preferably at the 5'-OH position of the nucleoside or lipophilic preparations, include U.S. Patent Nos. 5,149,794 (Sep. 22, 1992, Yatvin *et al.*); 5,194,654 (Mar. 16, 1993, Hostetler *et al.*, 5,223,263 (June 29, 1993, Hostetler *et al.*); 5,256,641 (Oct. 26, 1993, Yatvin *et al.*); 5,411,947 (May 2, 1995, Hostetler *et al.*); 5,463,092 (Oct. 31, 1995, Hostetler *et al.*); 5,543,389 (Aug. 6, 1996, Yatvin *et al.*); 5,543,390 (Aug. 6, 1996, Yatvin *et al.*); 5,543,391 (Aug. 6, 1996, Yatvin *et al.*); and 5,554,728 (Sep. 10, 1996; Basava *et al.*), all of which are incorporated herein by reference. Foreign patent applications that disclose lipophilic substituents that can be attached to the nucleosides of the present invention, or lipophilic preparations, include WO 89/02733, W0 90/00555, W0 91/16920, W0 91/18914, W0 93/00910, W0 94/26273, W0 96/15132, EP 0 350 287, EP 93917054.4, and W0 91/19721.

II. Combination and Alternation Therapy

It has been recognized that drug-resistant variants of HCV can emerge after prolonged treatment with an antiviral agent. Drug resistance most typically occurs by mutation of a gene that encodes for an enzyme used in viral replication. The efficacy of a drug against HCV infection can be prolonged, augmented, or restored by administering the compound in combination or alternation with a second, and perhaps third, antiviral compound that induces a different mutation from that caused by the principle drug. Alternatively, the pharmacokinetics, biodistribution, or other parameter of the drug can be altered by such combination or alternation therapy. In general, combination therapy is typically preferred over alternation therapy because it induces multiple simultaneous stresses on the virus.

Nonlimiting examples of antiviral agents that can be used in combination with the compounds disclosed herein include:

(1) an interferon and/or ribavirin (Battaglia, A.M. *et al.*, Ann. Pharmacother. 34:487-494, 2000); Berenguer, M. *et al.* Antivir. Ther. 3(Suppl. 3):125-136, 1998);

(2) Substrate-based NS3 protease inhibitors (Attwood *et al.*, *Antiviral peptide derivatives*, PCT WO 98/22496, 1998; Attwood *et al.*, *Antiviral Chemistry and Chemotherapy* 10.259-273, 1999; Attwood *et al.*, *Preparation and use of amino acid derivatives as anti-viral agents*, German Patent Pub. DE 19914474; Tung *et al. Inhibitors of serine proteases, particularly*

hepatitis C virus NS3 protease, PCT WO 98/17679), including alphaketoamides and hydrazinoureas, and inhibitors that terminate in an electrophile such as a boronic acid or phosphonate. Llinas-Brunet et al, *Hepatitis C inhibitor peptide analogues,* PCT WO 99/07734.

(3) Non-substrate-based inhibitors such as 2,4,6-trihydroxy-3-nitro-benzamide derivatives(Sudo K. *et al., Biochemical and Biophysical Research Communications,* 238:643-647, 1997; Sudo K. *et al. Antiviral Chemistry and Chemotherapy* 9:186, 1998), including RD3-4082 and RD3-4078, the former substituted on the amide with a 14 carbon chain and the latter processing a *para*-phenoxyphenyl group;

(4) Thiazolidine derivatives which show relevant inhibition in a reverse-phase HPLC assay with an NS3/4A fusion protein and NS5A/5B substrate (Sudo K. *et al., Antiviral Research* 32:9-18, 1996), especially compound RD-1-6250, possessing a fused cinnamoyl moiety substituted with a long alkyl chain, RD4 6205 and RD4 6193;

(5) Thiazolidines and benzanilides identified in Kakiuchi N. *et al. J. EBS Letters* 421:217-220; Takeshita N. *et al. Analytical Biochemistry* 247:242-246, 1997;

(6) A phenan-threnequinone possessing activity against HCV protease in a SDS-PAGE and autoradiography assay isolated from the fermentation culture broth of *Streptomyces* sp., Sch 68631 (Chu M. *et al., Tetrahedron Letters* 37:7229-7232, 1996), and Sch 351633, isolated from the fungus *Penicillium griscofuluum,* which demonstrates activity in a scintillation proximity assay (Chu M. *et al., Bioorganic and Medicinal Chemistry Letters* 9:1949-1952);

(7) Selective NS3 inhibitors based on the macromolecule elgin c, isolated from leech (Qasim M.A. *et al., Biochemistry* 36:1598-1607, 1997);

(8) HCV helicase inhibitors (Diana G.D. *et al., Compounds, compositions and methods for treatment of hepatitis C,* U.S. Pat. No. 5,633,358; Diana G.D. *et al., Piperidine derivatives, pharmaceutical compositions thereof and their use in the treatment of hepatitis C,* PCT WO 97/36554);

(9) HCV polymerase inhibitors such as nucleotide analogues, gliotoxin (Ferrari R. *et al. Journal of Virology* 73:1649-1654, 1999), and the natural product cerulenin (Lohmann V. *et al., Virology* 249:108-118, 1998);

(10) Antisense phosphorothioate oligodeoxynucleotides (S-ODN) complementary to sequence stretches in the 5' non-coding region (NCR) of the HCV (Alt M. *et al., Hepatology* 22:707-717, 1995), or nucleotides 326-348 comprising the 3' end of the NCR and nucleotides

371-388 located in the core coding region of the HCV RNA (Alt M. *et al.*, *Archives of Virology*, 142:589-599, 1997; Galderisi U. *et al.*, *Journal of Cellular Physiology* 181:251-257, 1999);

(11) Inhibitors of IRES-dependent translation (Ikeda N *et al.*, *Agent for the prevention and treatment of hepatitis C,* Japanese Patent Pub. JP-08268890; Kai Y. *et al. Prevention and treatment of viral diseases*, Japanese Patent Pub. JP-10101591);

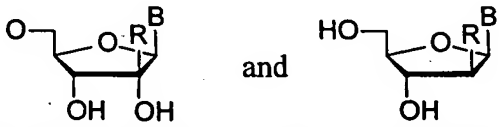
(12) Nuclease-resistant ribozymes. (Maccjak D.J. *et al.*, *Hepatology 30* abstract 995, 1999); and

(13) Other miscellaneous compounds including 1-amino-alkylcyclohexanes (U.S. Patent No. 6,034,134 to Gold *et al.*), alkyl lipids (U.S. Pat. No. 5,922,757 to Chojkier *et al.*), vitamin E and other antioxidants (U.S. Pat. No. 5,922,757 to Chojkier *et al.*), squalene, amantadine, bile acids (U.S. Pat. No. 5,846,964 to Ozeki *et al.*), N-(phosphonoacetyl)-L-aspartic acid, (U.S. Pat. No. 5,830,905 to Diana *et al.*), benzenedicarboxamides (U.S. Pat. No. 5,633,388 to Diana *et al.*), polyadenylic acid derivatives (U.S. Pat. No. 5,496,546 to Wang *et al.*), 2',3'-dideoxyinosine (U.S. Pat. No. 5,026,687 to Yarchoan *et al.*), and benzimidazoles (U.S. Pat. No. 5,891,874 to Colacino *et al.*).

III. Processes for the Preparation of Active Compounds

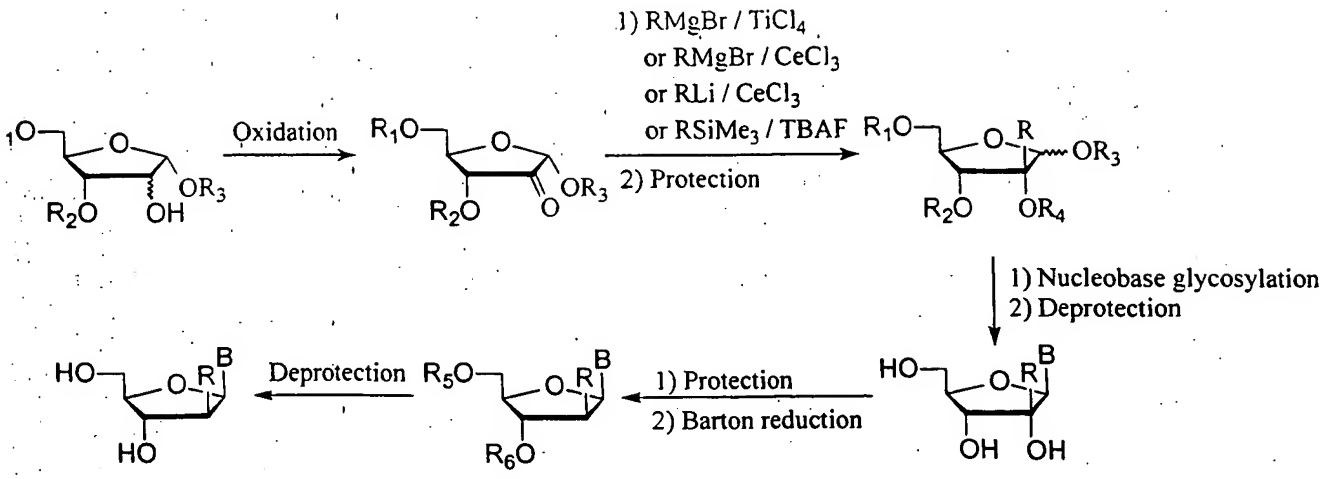
A. General Synthesis of 2'-C-Branched ribonucleosides and their 2'-deoxy derivatives.

2'-C-Branched ribonucleosides and their 2'-deoxy derivatives, of the structure:



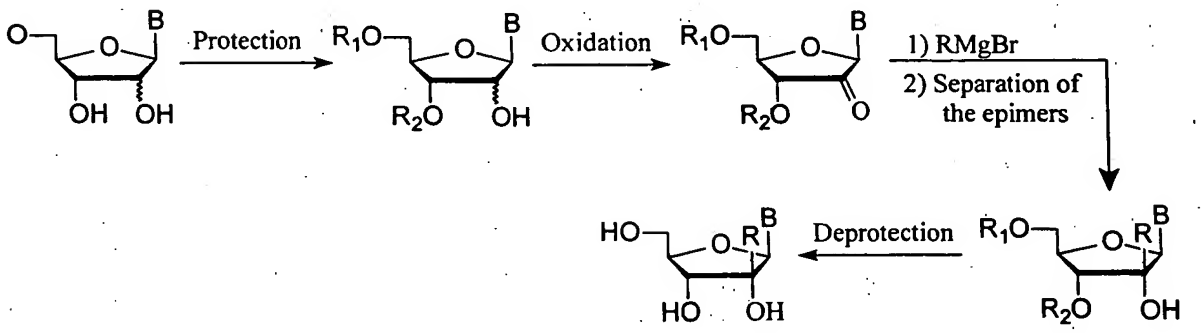
wherein B represents one of the five naturally occurring nucleobases, or a substituted purine or pyrimidine, and R is an alkyl, halogeno-alkyl (i.e. CF_3...), alkenyl, or alkynyl (i.e. allyl...), can be prepared by one of the following general methods.

Glycosylation of the nucleobase with an appropriately modified sugar



Wherein B is a nucleobase or a protected nucleobase, and R_1-R_6 are commonly used protecting groups.

Modification of a preformed nucleoside

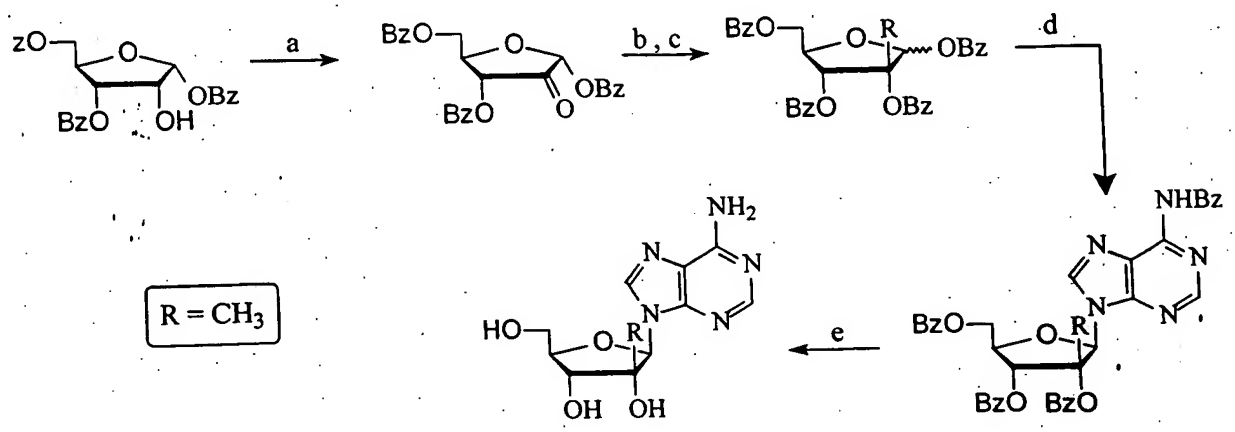


Wherein B is a nucleobase or a protected nucleobase, and R_1-R_2 are commonly used protecting groups.

Note : The L-enantiomers corresponding to the compounds of the invention can be prepared following the same foregoing general methods, beginning with the corresponding L-sugar or nucleoside L-enantiomer as starting material.

Example : Preparation of 2'-C-methylriboadenine

The title compound was prepared according to a published procedure (R.E. Harry-O'kuru, J.M. Smith, and M.S. Wolfe, "A short, flexible route toward 2'-C-branched ribonucleosides", *J.Org. Chem.* **1997**, 62, 1754-1759) (Scheme 1).

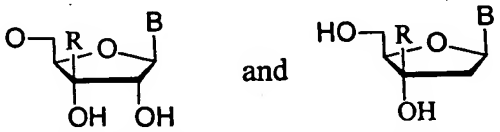


-Scheme 1-

(a) Dess-Martin periodinane; (b) MeMgBr / $TiCl_4$; (c) BzCl, DMAP, Et_3N; (d) bis(trimethylsilyl)acetamide, N^6-benzoyl adenine, TMSOTf; (e) NH_3 / MeOH

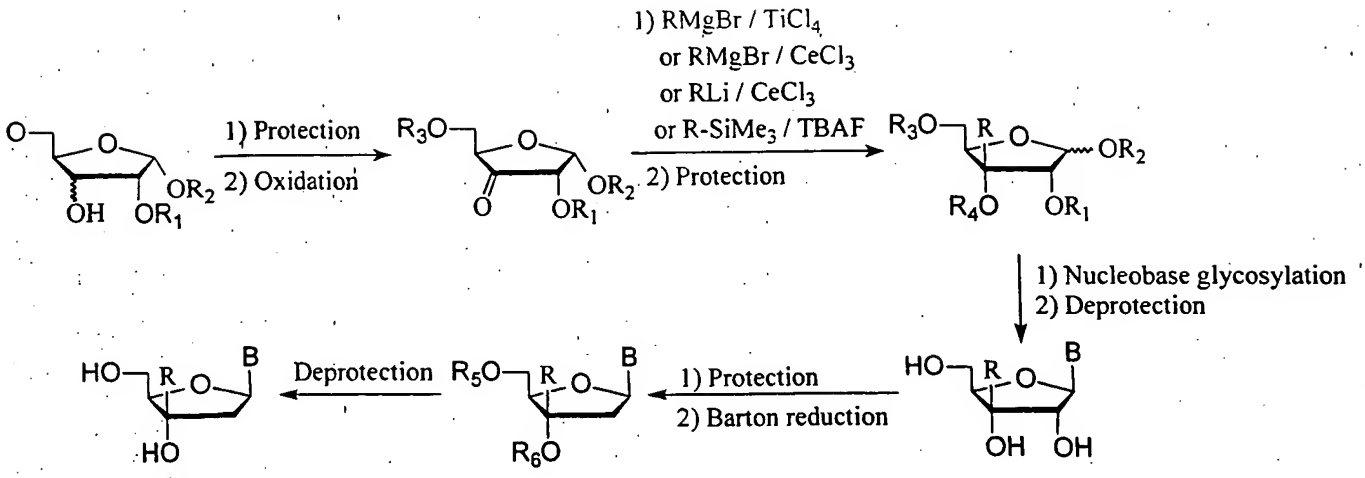
B. General Synthesis of 3'-C-Branched ribonucleosides and their 2'-deoxy derivatives.

3'-C-Branched ribonucleosides and their 2'-deoxy derivatives of the following structures



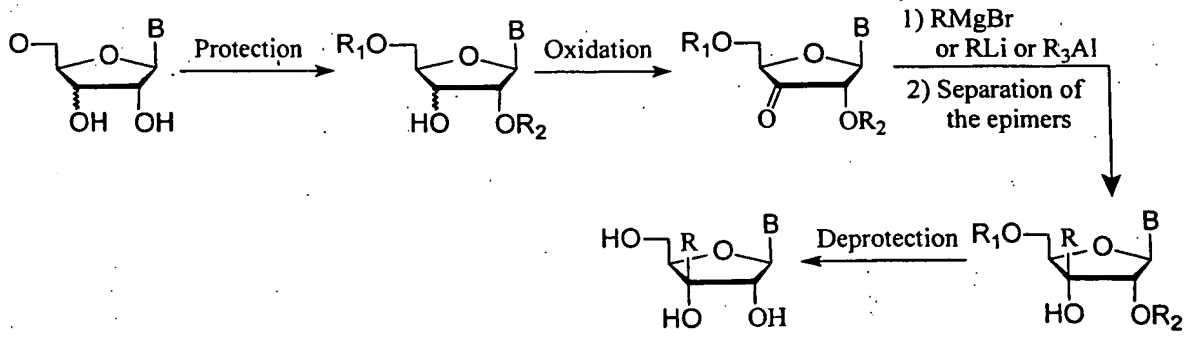
wherein B represents one of the five naturally occurring nucleobases, or a substituted purine or pyrimidine, and R is an alkyl, halogeno-alkyl (i.e. CF_3...), alkenyl, or alkynyl (i.e. allyl...), can be prepared generally according to the following synthetic schemes.

Glycosylation of the nucleobase with an appropriately modified sugar



wherein B is a nucleobase or a protected nucleobase, and R_1-R_6 are commonly used protecting groups.

Modification of a preformed nucleoside

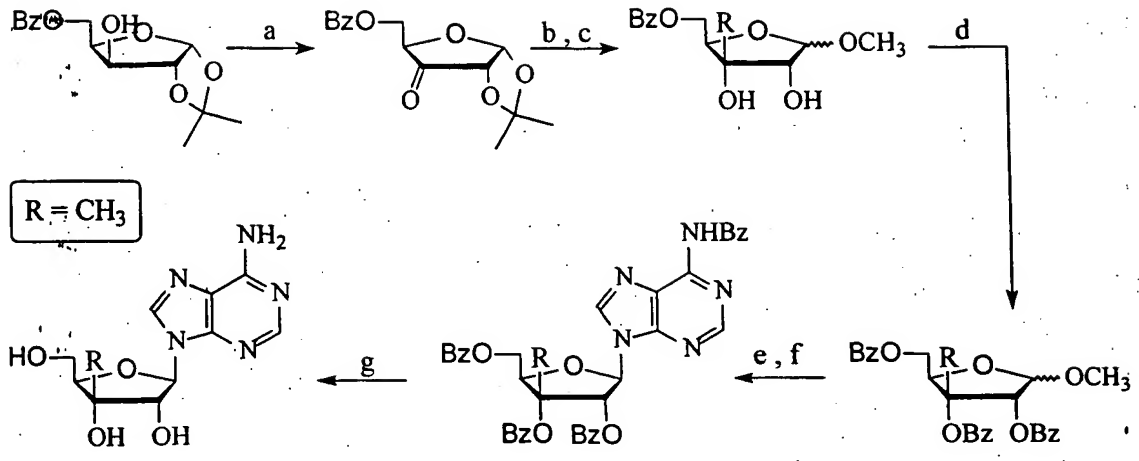


Wherein B is a nucleobase or a protected nucleobase, and R_1-R_2 are commonly used protecting groups.

Note : The L-enantiomers corresponding to the compounds of the invention can be prepared following the same A and B general methods, beginning with the corresponding L-sugar or nucleoside L-enantiomer as starting material.

Example : Preparation of 3'-C-methylriboadenine

The title compound can be prepared according to a published procedure (R.F. Nutt, M.J. Dickinson, F.W. Holly, and E. Walton, "Branched-chain sugar nucleosides. III. 3'-C-methyladenine", *J.Org. Chem.* **1968**, 33, 1789-1795) (Scheme 2).

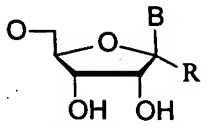


-Scheme 2-

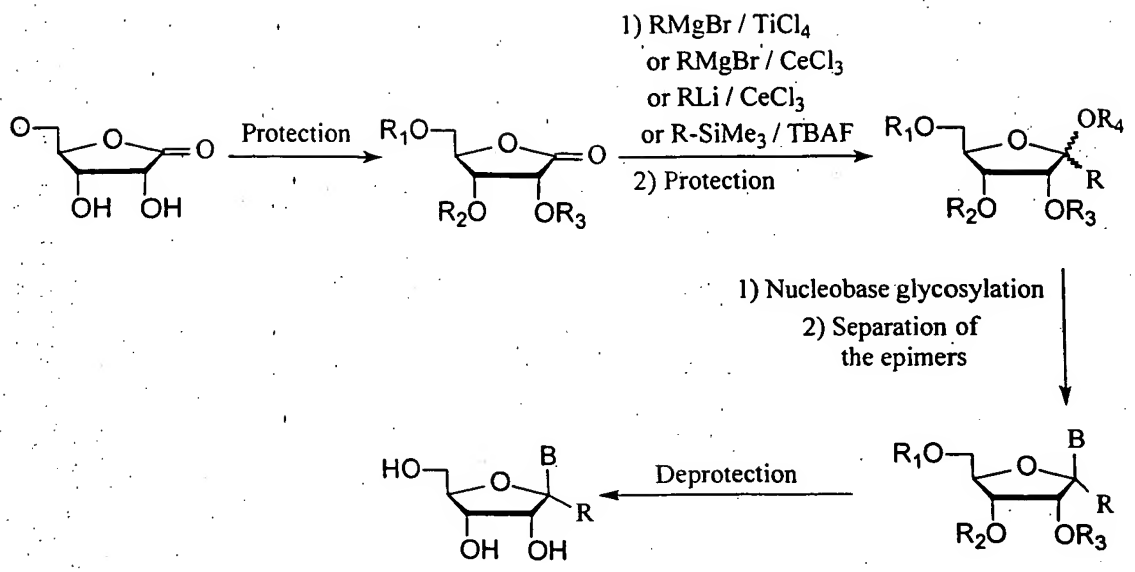
(a) RuO_2 / $NaIO_4$; (b) MeMgI / $TiCl_4$; (c) HCl / MeOH / H_2O; (d) BzCl / pyridine; (e) AcBr, HBr / AcOH; (f) chloromercuri-6-benzamidopurine; (g) NH_3 / MeOH.

C. General Synthesis of 1'-C-Branched ribonucleosides

1'-C-Branched ribonucleosides of the following structure:

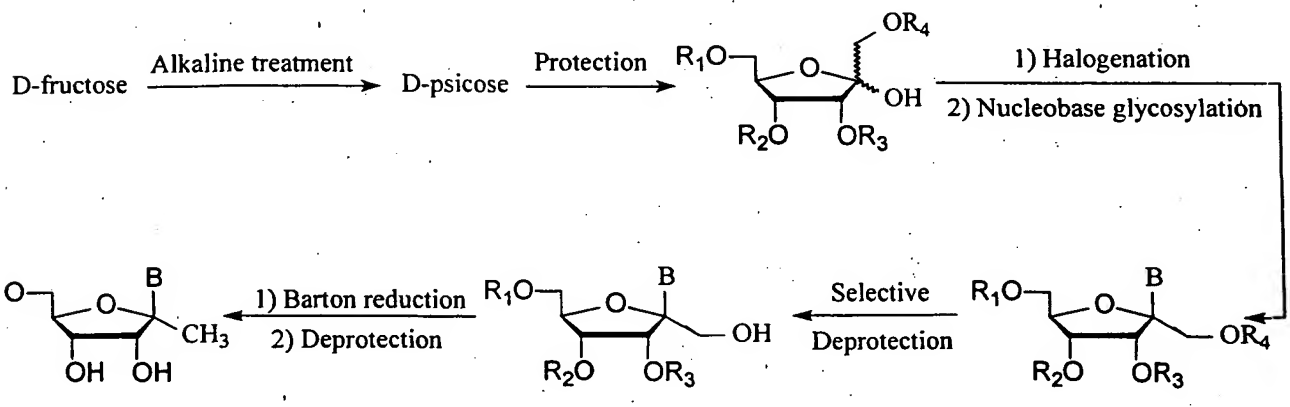


wherein B represents one of the five naturally occurring nucleobases, or a substituted purine or pyrimidine, and R is an alkyl, halogeno-alkyl (i.e. CF_3...), alkenyl, or alkynyl (i.e. allyl...), can be prepared by the following general method, starting from D-ribonolactone:



wherein B is a nucleobase or a protected nucleobase, and R_1-R_4 are commonly used protecting groups.

Alternative method for the preparation of 1'-C-methyl ribonucleosides

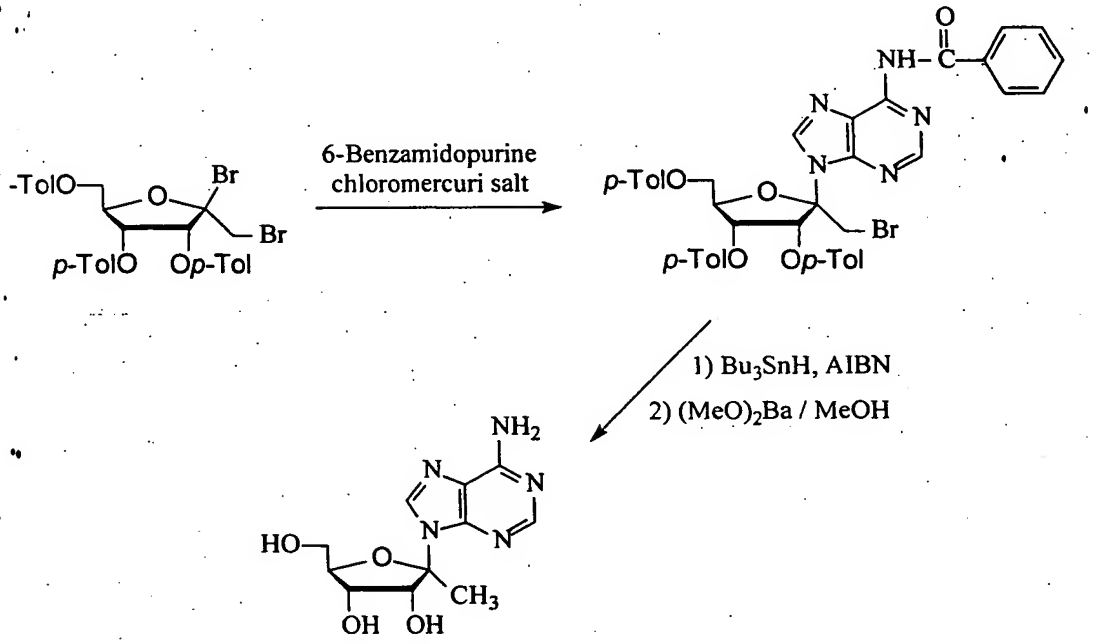


Wherein B is a nucleobase or a protected nucleobase, and R_1-R_4 are commonly used protecting groups.

Note : The L-enantiomers corresponding to the compounds of the invention can be prepared following the same A and B general methods, beginning with the corresponding L-sugar or nucleoside L-enantiomer as starting material.

Example : Preparation of 6-amino-9-(1-deoxy-β-D-psicofuranosyl)purine

As another alternative method of preparation, the title compound could also be prepared according to a published procedure (J. Farkas, and F. Sorm, "Nucleic acid components and their analogues. XCIV. Synthesis of 6-amino-9-(1-deoxy-β-D-psicofuranosyl)purine", *Collect. Czech. Chem. Commun.* **1967**, 32, 2663-2667. J. Farkas", *Collect. Czech. Chem. Commun.* **1966**, 31, 1535) (Scheme 3).



-Scheme 3-

IV. Anti-Hepatitis C Activity

Compounds can exhibit anti-hepatitis C activity by inhibiting HCV polymerase, by inhibiting other enzymes needed in the replication cycle, or by other known methods. A number of assays have been published to assess these activities. A general method that assesses the gross increase of HCV virus in culture is disclosed in U.S. Pat. No. 5,738,985 to Miles *et al.* In vitro assays have been reported in Ferrari *et al., Jnl. of Vir.*, 73:1649-1654, 1999; Ishii *et al.*, *Hepatology*, 29:1227-1235,1999; Lohmann *et al., Jnl. of Bio. Chem.*, 274:10807-10815, 1999; and Yamashita *et al, Jnl. of Bio. Chem.*, 273:15479-15486, 1998.

WO 97/12033, filed on September 27, 1996, by Emory University, listing C. Hagedorn and A. Reinoldus as inventors, and which claims priority to U.S.S.N. 60/004,383, filed on September 1995, describes an HCV polymerase assay that can be used to evaluate the activity of the compounds described herein. Another HCV polymerase assay has been reported by Bartholomeusz, *et al.*, Hepatitis C virus (HCV) RNA polymerase assay using cloned HCV non-structural proteins; Antiviral Therapy 1996:1(Supp 4) 18-24.

Screens that measure reductions in kinase activity from HCV drugs are disclosed in U.S. Pat. No. 6,030,785, to Katze *et al.*, U.S. Pat. No. 6,010,848 to Delvecchio et al, and U.S. Pat. No. 5,759,795 to Jubin *et al.* Screens that measure the protease inhibiting activity of proposed HCV drugs are disclosed in U.S. Pat. No. 5,861,267 to Su et al, U.S. Pat. No. 5,739,002 to De Francesco et al, and U.S. Pat. No. 5,597,691 to Houghton *et al.*

V. Pharmaceutical Compositions

Humans suffering from HCV can be treated by administering to the patient an effective amount of the active compound or a pharmaceutically acceptable prodrug or salt thereof in the presence of a pharmaceutically acceptable carrier or diluent. The active materials can be administered by any appropriate route, for example, orally, parenterally, intravenously, intradermally, subcutaneously, or topically, in liquid or solid form.

A preferred dose of the compound for HCV will be in the range from about 1 to 50 mg/kg, preferably 1 to 20 mg/kg, of body weight per day, more generally 0.1 to about 100 mg per kilogram body weight of the recipient per day. The effective dosage range of the pharmaceutically acceptable salts and prodrugs can be calculated based on the weight of the parent nucleoside to be delivered. If the salt or prodrug exhibits activity in itself, the effective dosage can be estimated as above using the weight of the salt or prodrug, or by other means known to those skilled in the art.

The compound is conveniently administered in unit any suitable dosage form, including but not limited to one containing 7 to 3000 mg, preferably 70 to 1400 mg of active ingredient per unit dosage form. A oral dosage of 50-1000 mg is usually convenient.

Ideally the active ingredient should be administered to achieve peak plasma concentrations of the active compound of from about 0.2 to 70 pM, preferably about 1.0 to 10 μM. This may be achieved, for example, by the intravenous injection of a 0.1 to 5% solution of the active ingredient, optionally in saline, or administered as a bolus of the active ingredient.

The concentration of active compound in the drug composition will depend on absorption, inactivation, and excretion rates of the drug as well as other factors known to those of skill in the art. It is to be noted that dosage values will also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed composition. The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at varying intervals of time.

A preferred mode of administration of the active compound is oral. Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable prodrug or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti-inflammatories, or other

antivirals, including other nucleoside compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

In a preferred embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyanhydrides, polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation.

Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) are also preferred as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art, for example, as described in U.S. Patent No. 4,522,811 (which is incorporated herein by reference in its entirety). For example, liposome formulations may be prepared by dissolving appropriate lipid(s) (such as stearoyl phosphatidyl ethanolamine, stearoyl phosphatidyl choline, arachadoyl phosphatidyl choline, and cholesterol) in an inorganic solvent that is then evaporated, leaving behind a thin film of dried lipid on the surface of the container. An aqueous solution of the active compound or its monophosphate, diphosphate, and/or triphosphate derivatives is then introduced into the container. The container is then swirled by hand to free lipid material from the sides of the container and to disperse lipid aggregates, thereby forming the liposomal suspension.

This invention has been described with reference to its preferred embodiments. Variations and modifications of the invention, will be obvious to those skilled in the art from the foregoing detailed description of the invention.